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09/467,901	12/21/1999	JOOST VAN NEERVEN	02405.0190	2936

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EXAMINER

DO, PENSEE T

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/467,901

Applicant(s)

NEERVEN, JOOST VAN

Examiner

Pensee T. Do

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 September 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6 and 8-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Amendment Entry & Claim Status***

The amendment filed on September 26, 2003 has been acknowledged and entered.

Claims 1-6, 8-22 are pending.

***Withdrawn Rejection(s)***

Rejections under 35 USC 112, 1<sup>st</sup> and 2<sup>nd</sup> paragraph in the previous office action are withdrawn herein.

Rejection under 35 USC 102 is withdrawn herein.

Rejection under 35 USC 103 by Johansen in view of Johnson and Frank 2 for *claim 15* is withdrawn herein.

***Newgrounds of Rejection(s)***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims, 1, 6, 8-16, 21, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims, 1, 6, 21, 22 are indefinite. It is unclear of where the label is attached. To which components in parts a, b, c does the label attach? For example in part (a), the label can be attached to either the IgE antibody or the ligand; in part (b), the label can be attached to the IgE receptor; in part (c), where is the label supposed to be?

***Maintained Rejection(s)***

***Claim Rejections - 35 U.S.C. 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1-5, 8-14, 16, 21, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) further in view of Johnson et al. (US 6,034,066) and Frank et al. (US 6,060,326).

Johansen et al. teach a method of detecting an antibody in a sample using a labeling compound and comprising the steps of mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to a paramagnetic particles; and a chemiluminescent acridinium compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex. There are several embodiments. In one embodiment, the method comprises the following steps: mixing the ligand antigen, antibody or hapten bound to biotin or a functional derivative thereof with the sample and the antibody directed against the antibody to be detected bound to paramagnetic particles to form a first solid phase complex; adding a chemiluminescent acridinium

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compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex; magnetically separating the solid phase from the liquid phase; initiating the chemiluminescent reaction, and analyzing the separated solid phase for the presence of the chemiluminescent complex. Johansen et al. also teaches the method for the quantification of specific antibodies, such as immunoglobulins, wherein a truly parallel reference immunoassay using an identical protocol as a reference. The method comprises measuring the concentration and/or the relative contents of a specific antibody in a liquid sample, wherein the measured light emission of a separated solid phase comprising a captured specific antibody coupled to a chemiluminescent label is compared with the measured light emission obtained in a parallel reference immunoassay wherein the total contents of the class of antibodies in the sample to which said specific antibody belongs is measured. The method comprising the steps of mixing a ligand antigen, hapten towards which the specific antibody to be measured is directly bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the antibody to be measured bound to paramagnetic particles and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof with the sample to form a first solid phase from the liquid phase; magnetically separating the first solid phase from the liquid phase; initiating a chemiluminescent reaction and measuring the light emission of the separated first solid phase; mixing a ligand antibody directed against the class of antibodies to be measured bound to biotin or a functional derivative thereof ; an antibody directed against the constant portion of the class of antibodies to be measured

bound to paramagnetic particles ; and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof wherein the term total shall mean the entire amount of the designated class of immunoglobulins (e.g. IgA, IgE, etc.) With the sample to form a second solid phase complex, magnetically separate the second solid phase from the liquid phase; initiating the light emission of the separated first solid phase with that of the separated second solid phase. The specific antibody to be measured in the sample is preferably a specific immunoglobulin selected from the group consisting of IgA, IgD, IgE, IgG, IgM and subclasses thereof. (See col. 3, line 30-col. 5, line 45).

However, Johansen et al. fails to teach using an IgE receptor to bind IgE antibody/ligand complexes and a method of quantification of IgE wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using Fc0RII alone to obtain a second measurement.

Johnson et al. teach multiple important roles of CD23 in the regulation of immune responses, particularly the regulation of IgE responses. Among these roles, CD23 acts as a cellular receptor for IgE and is found in various cell types including B cells. (See col. 1, line 31-col. 2, line 64).

Frank et al. teach detecting IgE antibodies using a human Fc epsilon receptor Fc0R. (See col. 1, line 45-col. 2, line 10).

It would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson et al. and Frank et al. to measure IgE according to the method of Johansen et al. since both of these receptors, CD23 and Fc0R, are specific to IgE

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antibody and because Fc0R and CD23 can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (See Frank et al. Col. 1, lines 19-34). Regarding claim 16, wherein the number of ligand molecules is between 100% and 200 % of the number of IgE molecules to be detected, it would have been obvious to one of ordinary skills in the art to use enough ligand molecules to optimize binding of all the IgE molecules to be detected. In order to detect 100% of the IgE present in the sample, at least 100% of ligand molecules must be present to bind all the IgE present in the sample.

argue that Frank used an antigen (ligand) that was fixed to a plastic bead. The instant invention uses a free, dissolved ligand. Thus, Frank does not disclose all the claimed invention's elements and cannot anticipate claims 1, 17-19.

Frank teaches that the ligand is bound to a plastic bead, and the plastic bead is also labeled with a colorimetric marker. In operation, when the sample contacts the labeled ligand bound plastic bead in the labeling zone, the labeled ligand bound plastic bead dissolves and moves freely along the flow path to the capture region wherein the IgE (analyte to be detected in the sample)-labeled ligand bound plastic bead is captured by an IgE receptor - FcεR molecule. The capturing step is also the separation step of complexes from the non-complexes. Thus, Frank meets the requirement of the claimed invention of a free-dissolved ligand. Since the claims contain opening language, the beads can be interpreted as part of the label.

Claims 6, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) in view of Frank et al. (US 6,060,326) further in view of Arnold, Jr. et al. (US 6,004,745).

Johansen et al. and Frank et al. have been discussed above.

However, Johansen and Frank fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels.

Arnold, Jr. discusses in the background section that a typical sandwich assay involve incubating an immobilized antibody (IgE receptor) with a test medium (sample). Antigens, if in the medium, will bind to the antibody. After incubation, unbound antigen is removed in a separation step. After a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched between the immobilized antibody and the labeled antibody. After a second separation step, the amount of labeled antibody can be determined as a measure of the antigen in the medium. (see col. 1, lines 55-66).

It would have been obvious to one of ordinary skill in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold, Jr. using the reagents in the method of Johansen modified by Frank because such second separation steps, although time consuming, increases the sensitivity of the assay results. Furthermore, since the non-complexed immobilized antibody and the non-complexed labels are separated one at a time, cross-reactivity between the label and the immobilized antibody/reagent is eliminated.

***Response to Arguments***



The arguments filed on September 26, 2003 have been fully considered but not found persuasive.

Regarding the 103 rejection by Johansen, Applicants argue that Johansen's general discussion of the assays described therein does not provide the necessary motivation to develop an assay using IgE receptors. Johnson's general discussion of the roles CD23 may play in immune responses does not motivate the skilled artisan to develop the claimed IgE detection method. Frank 2 provides no motivation for developing methods that use both a free dissolved ligand and a carrier to which is bound an IgE receptor. As such, these references cannot provide the requisite motivation. Applicants also argue that the Office fails to provide proof for supporting the rejection of claim 16 that it would have been obvious to use enough ligand molecules to optimize the binding of all the IgE molecules to be detected.

The motivation to combine the references has been clearly established in the previous office action. Johansen teaches a method for the quantification of specific antibodies such as immunoglobulins (IgE, IgA, ..). The sample containing the specific antibody is mixed with a ligand antigen (free dissolved ligand of the present invention); an antibody directed against a constant portion of the antibody to be measured bound to a paramagnetic particles and a chemiluminescent acridinium compound as a label; magnetically separating the bound from the unbound; and detect. Johnson uses a CD23 which is specific for IgE antibody. Frank teaches detecting IgE antibodies using a human Fc epsilon receptor (Fc0R). Thus, it would have been obvious to one of ordinary skill in the art to use CD23 or Fc0R as an IgE receptor to measure IgE antibody

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because these receptors can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. Regarding claim 16, it is obvious for an ordinary skill in the art to optimize the result by binding all the IgE molecules to be detected.

Regarding the 103 rejection by Johansen in view of Frank 2 and Arnold, Applicants argue that Arnold does not cure the deficiency of motivation as discussed above. The assay of Arnold employs antibodies that are immobilized. The claimed invention allow binding reactions between IgE and ligand to take place in solution without the involvement of an immobilizing agent. Because these methods are not comparable, Arnold cannot cure the lack of motivation in Johansen and Frank 2 to develop the claimed method. Moreover, Applicants submit that Arnold teaches away from heterogeneous assay by developing a homogeneous assay, which does not require a separation step. Since the present invention includes at least one separation step, Arnold is inapplicable.

In col. 2, lines 16-20, Arnold teaches that "it is also an object of this invention to provide improved *methods for increasing the sensitivity of assays which involve separation* by combining the homogeneous method disclosed with other *separation* method to reduce non-specific background". Thus, Arnold's invention also includes a heterogeneous assay which has a separation step. (emphases added).

### **Conclusion**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 703-308-4398. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Pensee T. Do  
Patent Examiner  
December 5, 2003



CHRISTOPHER L. CHIN  
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